REMARKS

Claims 1, 2, 21, 22, and 48-67 are pending in the application. Claims 3-20 and 23-47 have been cancelled without prejudice. Claims 1, 21, and 22 have been amended. New claims 48-67 have been added. Support for the amendments and new claims can be found in original claims 2 and 13 and in original claims 1, 2, 7, 8, 18, and 22 and in the specification at, e.g., page 4, line 26, to page 5, line 5; page 16, line 28, to page 17, line 4; and page 18, line 26, to page 19, line 20;. These amendments add no new matter.

35 U.S.C. §112, First Paragraph (Enablement)

At pages 2-5 of the Office Action, claims 1-4, 17-24, and 27-29 were rejected as not enabled. According to the Office Action, "the specification, while being enabling for reducing oxidative stress-associated cell death, does not reasonably provide enablement for preventing oxidative stress-associated cell death." The claims have been amended to remove the term "preventing," thereby obviating the present rejection.

35 U.S.C. §112, Second Paragraph (Indefiniteness)

At pages 5-6 of the Office Action, claim 27 was rejected as indefinite. Claim 27 has been cancelled without prejudice, thereby obviating the present rejection.

35 U.S.C. §103(a) (Obviousness)

At pages 7-10 of the Office Action, claims 1-4, 17, 18, 21-24, and 27-29 were rejected as unpatentable over Gambacorti-Passerini et al., WO 01/47507 ("Gambacorti") in view of Kumar et al. (2001) J. Biol. Chem 276:17281-85 ("Kumar") and Kufe et al., U.S. Patent No. 7,118,862 ("Kufe").

The claimed methods are based at least in part on the inventors' discovery that the tyrosine kinase inhibitor STI571 can be used to prevent cell death associated with oxidative stress. As detailed in the specification, STI571 was previously known to be highly effective in the treatment of chronic myelogenous leukemia ("CML") and induces apoptosis of CML cells in

culture. In contrast, the experimental data contained in the present application demonstrates that STI571 inhibits ROS-induced apoptosis. The finding that STI571 inhibits apoptosis was unexpected in light of the molecule's prior characterization as an effective inducer of apoptosis in cells derived from CML patients.

Consistent with the inventors' unexpected findings summarized above, independent claims 1 and 51 are directed to methods of treating a myocardial infarction (claim 1) or a stroke (claim 51) by administering to an individual in need thereof a therapeutically effective amount of a composition comprising an N-phenyl-2-pyrimidine-amine. As detailed in the specification, myocardial infarction and stroke are disorders characterized by excessive oxidative stress-associated cell death.

Gambacorti discloses the use of STI571 for the treatment of proliferative diseases. As noted above, STI571 was understood at the time the present application was filed to be useful for the treatment of proliferative diseases such as CML. Gambacorti (at page 37, last paragraph extending to the top of page 38) reflects the understanding of STI571 as a compound that induces apoptosis:

> STI571 (formerly known as CGP57148) represents an active and relatively specific inhibitor of bcr/abl kinase activity. STI571 blocks proliferation and induces apoptosis in BCR/ABL+ cells *in vitro*; it inhibits the growth of clonogenic bone marrow cells obtained from CML patients, and can eradicate leukemic cell growth *in vivo*. (emphasis added)

The person of ordinary skill in the art having read Gambacorti would have had no reason to expect that a compound (such as STI571) that induces apoptosis (and is useful for treating disorders such as proliferative diseases that are characterized by insufficient cell death) would be useful in inhibiting apoptosis and treating disorders characterized by excessive oxidative stress-associated cell death. Kumar and Kufe do not cure the deficiencies of Gambacorti. Kumar describes the targeting of c-Abl to the mitochondria in the cell death response to oxidative stress. Kufe is the patent counterpart of the Kumar academic publication (i.e., the experimental results of Kumar are described within Example 4 of Kufe). Kufe describes screenings assays and methods of treatment based on the modulation of translocation of c-Abl to the mitochondria.

Nowhere does Kumar or Kufe suggest inhibiting c-Abl kinase activity as a means of modulating oxidative stress-associated cell death. The references describe the importance of cellular localization of c-Abl to cell death processes, but provide no hint that inhibition of c-Abl activity may be an effective means of preventing cell death associated with oxidative stress. As a result, the combined teachings of Gambacorti, Kumar, and Kufe would not have led the person of ordinary skill in the art at the time the present application was filed to reasonably expect that STI571 could be used in the treatment of myocardial infarction and stroke, disorders characterized by excessive oxidative stress-associated cell death.

In view of the foregoing, Gambacorti, Kumar, and Kufe do not render obvious independent claims 1 or 51 or the claims that depend directly or indirectly therefrom. Applicants respectfully request that the Examiner withdraw the rejection.

At pages 10-11 of the Office Action, claims 19 and 20 were rejected as unpatentable over Gambacorti in view of Kumar and Kufe, and further in view of Robinson et al., U.S. Patent No. 5,135,945.

Claims 19 and 20 have been cancelled without prejudice, thereby obviating the present rejection.

CONCLUSIONS

Applicants submit that all grounds for rejection have been overcome, and that all claims are in condition for allowance, which action is requested.

Enclosed is a Petition for Three Month Extension of Time. The extension of time fee in the amount of $555 is being paid concurrently herewith on the Electronic Filing System (EFS) by way of Deposit Account authorization. Please apply any charges or credits to Deposit Account No. 06-1050, referencing Attorney Docket No. 00530-0108US1.

Respectfully submitted,

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